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# Influence of Cardiorespiratory Fitness on the Association between C-Reactive Protein and Metabolic Syndrome Prevalence in Racially Diverse Women

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## ABSTRACT

**Background:** Metabolic syndrome and C-reactive protein (CRP) are independent predictors of cardiovascular disease (CVD) among women. The extent to which cardiorespiratory fitness influences the relationship between CRP and metabolic syndrome is unknown.

**Methods and Results:** Cross-sectional associations among fitness, CRP, and metabolic syndrome were examined in 135 African American, Native American, and Caucasian women ( $55 \pm 11$  years,  $28 \pm 6$  kg/m<sup>2</sup>). Fitness was quantified with a symptom-limited maximal treadmill exercise test. Plasma CRP concentrations were determined with the Dade-Behring high-sensitivity immunoassay. Metabolic syndrome was defined according to NCEP-ATP III. Metabolic syndrome, CRP, and fitness varied ( $p < 0.05$ ) by race. Race-adjusted CRP values were directly associated ( $p < 0.05$ ) with each metabolic syndrome component. After adjusting for age and race, the relative odds of metabolic syndrome was 3.6 (95% CI = 1.5 – 8.4) in women with elevated ( $>2.0$  mg/L) vs. low CRP. Adjustment for smoking, hormone therapy, body mass index (BMI), and HOMA insulin resistance did not eliminate this association ( $p < 0.05$ ). The association between CRP and the metabolic syndrome was no longer significant (OR = 1.3, 95% CI = 0.9 – 5.9,  $p = 0.59$ ) after adjustment for fitness.

**Conclusions:** Higher cardiorespiratory fitness may be an important consideration in the milieu of vascular inflammation and metabolic syndrome.

## INTRODUCTION

ACCUMULATING EVIDENCE INDICATES that C-reactive protein (CRP), a marker of subclinical inflammation, independently predicts the risk of cardiovascular disease (CVD)<sup>1</sup> and diabetes<sup>2</sup> among women. A strong relationship has also been shown for CRP with the prevalence<sup>3</sup> and development<sup>4</sup> of the metabolic syndrome in wo-

men. The metabolic syndrome characterizes co-existing high-risk phenotypes of hypertension, dyslipidemia, insulin resistance, and central obesity<sup>5</sup> that multiplicatively increase the risk of CVD<sup>6</sup> and diabetes.<sup>7</sup> Two recent studies showed that the combination of elevated CRP and metabolic syndrome synergistically increased the risk of cardiovascular events and diabetes beyond that of either variable alone.<sup>8,9</sup> Chronic inflam-

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mation and the loss of metabolic homeostasis, as indicated by the metabolic syndrome, are potent cardiovascular antecedents and, when coexisting, identify an individual at high risk for a future event. Effective management of elevated CRP and metabolic syndrome may, therefore, have significant implications for the clinical and public health burden of CVD.

Physical activity is associated with lower cardiovascular and diabetes risk and improved risk factor profiles for both conditions.<sup>10</sup> Studies have shown that physical activity is inversely related to CRP<sup>11,12</sup> and to metabolic syndrome.<sup>13,14</sup> We reported<sup>15</sup> an inverse association between cardiorespiratory fitness, an objective measure of recent physical activity patterns,<sup>16</sup> and CRP,<sup>11</sup> as well as metabolic syndrome,<sup>13</sup> in a cohort of racially diverse, healthy, middle-aged women in the Cross-Cultural Activity Participation Study (CAPS). To our knowledge, the influence of activity or fitness on the association between CRP and metabolic syndrome has not yet been examined. In the current study, we report cross-sectional associations among fitness, CRP, and metabolic syndrome in a racially diverse sample of women.

## MATERIALS AND METHODS

Subjects were 44 African American, 45 Native American, and 46 Caucasian women who volunteered to participate in CAPS. The primary aim of CAPS was to develop physical activity surveys for diverse populations of women.<sup>11,13,15–17</sup> CAPS inclusion criteria were self-reported African American, Native American, or Caucasian ethnicity, absence of symptomatic disease, and absence of conditions that would preclude daily physical activity.<sup>15</sup> Interview-based health histories, body mass index (BMI, kg/m<sup>2</sup>), waist girth (cm), and resting blood pressure (BP) measures have been described.<sup>11,13,15–17</sup>

Following a 12-hour fast and 24-hour abstinence from exercise and smoking, antecubital blood was collected in EDTA, centrifuged, and frozen at  $-80^{\circ}\text{C}$  until analysis. Plasma CRP concentrations were measured with the Dade-Behring high-sensitivity immunoassay,<sup>11</sup> and elevated CRP was defined as  $>2.0$  mg/L.<sup>1</sup> We recognize that this CRP cut point is lower than that currently recommend to define high risk.<sup>18</sup> In the present analysis, a CRP level of  $>2.0$  mg/L is not meant to imply high risk but rather to identify wo-

men whose CRP is elevated above a level considered to be normal or low risk (1.0 mg/L).<sup>1,18</sup> A CRP value of 2.0 mg/L approximates the median CRP in our sample of women, and this definition of elevated CRP is used to maintain consistency with previously reported data from our study.<sup>11,17</sup> Plasma triglyceride, high-density lipoprotein (HDL) cholesterol, glucose, and insulin concentrations were obtained with standard automated bioassay procedures described elsewhere.<sup>17</sup> Insulin resistance was quantified using the homeostasis model assessment<sup>19</sup> (HOMA-IR). The Framingham 10-year probability<sup>16</sup> was used as a surrogate of coronary risk and analyzed categorically at  $>75$ th percentile, which equates to a 10-year probability  $>6.0\%$  among the apparently healthy asymptomatic cohort of CAPS women.

Metabolic syndrome was defined according to National Cholesterol Education Program (NCEP)-ATP III criteria<sup>5</sup> as  $\geq 3$  of the following: abdominal obesity (waist girth  $>88$  cm), low HDL ( $<50$  mg/dl), high triglyceride ( $\geq 150$  mg/dl), high glucose ( $\geq 110$  mg/dl), and high BP ( $\geq 130/85$  mm Hg).

Fitness was quantified as the duration of a physician-supervised maximal treadmill exercise test consisting of 2-minute stages graded by 1 MET per stage<sup>11,16</sup>. Maximal exertion was seen as achieving  $\geq 85\%$  age-predicted maximal heart rate and perceived exertion  $\geq 17$  on a 20-point Borg scale. Fitness was standardized to age-adjusted maximal METs (1 MET =  $3.5 \text{ ml O}_2 \text{ uptake} \cdot \text{kg body mass}^{-1} \cdot \text{min}^{-1}$ ) based on the final treadmill speed and grade.<sup>11</sup> Women who achieved  $\geq 8.5$  METs during the treadmill test were considered to be fit, and women who achieved  $<8.5$  METs were considered to be unfit. This MET value was used as a cut point because it approximates a level of fitness associated with significant cardiovascular risk reduction among women.<sup>20</sup>

Summary statistics (mean, SD, frequencies) were computed for variables in general accord with the assumptions of normal distribution. CRP, HOMA-IR, triglyceride, and glucose were skewed; therefore, these variables were log (Ln) transformed, and geometric means are reported descriptively. Differences in CRP concentrations according to risk factor levels, metabolic syndrome status, and fitness were examined with the general linear model. Differences in proportions were examined with chi-square analyses. Logistic regression was used to examine crude and covariate adjusted associations between CRP and

TABLE 1. CHARACTERISTICS OF STUDY PARTICIPANTS

	African Americans	Native Americans	Caucasian
<i>n</i>	44	45	46
Age, years <sup>a</sup>	56.6 ± 10	50.1 ± 9*	54.3 ± 10
BMI, kg/m <sup>2a</sup>	30.9 ± 6	28.7 ± 6	25.2 ± 5*,**
Waist, cm <sup>a</sup>	89.0 ± 13	88.9 ± 12	78.4 ± 11*,**
Systolic BP, mm Hg <sup>a</sup>	129.2 ± 18	118.2 ± 13*	116.3 ± 19*
Diastolic BP, mm Hg <sup>a</sup>	79.4 ± 9	76.7 ± 9	76.6 ± 9
Triglyceride, mg/dl <sup>b</sup>	81.7 ± 0.06	114.2 ± 0.07*	99.2 ± 0.07
HDL, mg/dl <sup>a</sup>	65.3 ± 19	50.9 ± 14*	57.6 ± 14**
Glucose, mg/dl <sup>b</sup>	91.6 ± 0.03	91.2 ± 0.04	84.4 ± 0.02
Insulin, pmol/L <sup>b</sup>	66.4 ± 0.09	56.4 ± 0.11	36.8 ± 0.09*,**
HOMA-IR <sup>b</sup>	15.8 ± 0.09	13.7 ± 0.13	8.6 ± 0.09*,**
CRP, mg/L <sup>b</sup>	4.3 ± 0.3	2.5 ± 0.3*	2.3 ± 1.3*
Framingham score, % <sup>a</sup>	4.6 ± 0.41	4.3 ± 0.50	4.3 ± 0.55
Treadmill time, min <sup>a</sup>	11.0 ± 2.7	13.5 ± 3*	15.7 ± 3*,**
Maximal METs <sup>a</sup>	7.2 ± 1	9.1 ± 2*	10.0 ± 2*,**
Current smoker, %	8.7	4.4	6.5
Hormone replacement, %	47.8	11.1*	47.8**
Abdominal obesity, %	51	47	17*,**
Low HDL, %	17	53*	29*
High triglyceride, %	4	27*	19*
High glucose, %	15	20	1*,**
High BP, %	70	38*	32*

<sup>a</sup>Mean ± SD.<sup>b</sup>Geometric mean ± SE.\**p* < 0.05 with African American; \*\**p* < 0.05 with Native American.

metabolic syndrome. Women with a CRP ≤2.0 mg/L were the referent group. All multivariable analysis controlled for age and race. Additional adjustment for hormone replacement therapy (HRT), BMI, HOMA-IR, and cardiorespiratory fitness was performed by entering each of these variables into separate models that already included CRP, age, and race. There were 12 women who self-reported a history of diabetes. After excluding these women and repeating the analysis, our primary findings were unchanged. Therefore, results are reported for the entire study sample including the women with diabetes. *p* values are two-sided, and *p* < 0.05 was accepted as statistically significant.

## RESULTS

Participants were middle-aged and overweight and had relatively low coronary heart disease (CHD) risk factors (Table 1). Among all women, the prevalence of metabolic syndrome, elevated CRP, combined elevated CRP and metabolic syndrome, and a ≥8.5 MET level of fitness was 22.6%, 45.9%, 17.8%, and 50.4%, respectively. The prevalence of these phenotypes varied significantly by race (Table 2). Crude and race-adjusted geometric mean CRP values were significantly higher among women stratified on the presence of metabolic syndrome and each of its components, fasting insulin, HOMA-IR, and fitness

TABLE 2. PREVALENCE OF METABOLIC SYNDROME, ELEVATED CRP, AND FITNESS BY RACE

	African American		Native American		Caucasian	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Metabolic syndrome	13	29.5	13	28.8	5	8.9*,**
Elevated CRP						
>2.0 mg/L	31	70.5	20	44.4*	13	28.2*,**
Metabolic syndrome and elevated CRP	10	22.7	11	24.4	2	4.3*,**
Fitness ≥8.5 METs	8	18.2	24	53.3*	35	76.1*,**

\**p* < 0.05 with African American; \*\**p* < 0.05 with Native American.

TABLE 3. CRP<sup>a</sup> (MG/L) CONCENTRATIONS ACCORDING TO RISK FACTOR CATEGORY

	<i>Unadjusted</i>	<i>Race adjusted</i>
Waist, cm		
≤88	2.5 ± 0.2	2.4 ± 0.3
>88	4.2 ± 0.3*	3.9 ± 0.3*
Blood pressure, mm Hg		
<130/85	2.2 ± 0.2	2.3 ± 0.2
≥130/85	4.8 ± 0.3*	4.7 ± 0.1*
Triglyceride, mg/dl		
<150	2.9 ± 0.2	2.8 ± 0.2
≥150	3.9 ± 0.5*	4.0 ± 0.4*
HDL, mg/dl		
≥50	2.8 ± 0.2	2.7 ± 0.2
<50	3.4 ± 0.4	3.3 ± 0.2
Glucose, mg/dl		
<110	2.5 ± 0.2	2.7 ± 0.2
≥110	6.3 ± 0.6*	4.9 ± 0.5*
Insulin, pmol/L <sup>b</sup>		
<44	2.2 ± 0.3	2.5 ± 0.3
≥44	3.9 ± 0.2*	3.5 ± 0.2*
HOMA-IR <sup>b</sup>		
<9.8	2.0 ± 0.3	2.2 ± 0.3
≥9.8	4.3 ± 0.3*	3.9 ± 0.2*
Metabolic syndrome		
Absent	2.6 ± 0.2	2.6 ± 0.2
Present	4.8 ± 0.4*	4.2 ± 0.4*
Fitness		
<8.5 METs	3.8 ± 0.3	3.4 ± 0.3
≥8.5 METs	2.4 ± 0.4*	2.5 ± 0.2*

<sup>a</sup>Data are geometric mean ± SE.

\* $p < 0.05$ .

<sup>b</sup>Cut point for HOMA-IR is based on a median split among women without diabetes or impaired fasting glucose.

(Table 3). The proportion of women with elevated CRP, metabolic syndrome, or both was higher ( $p \leq 0.005$ ) among unfit than fit women (Table 4). The proportion of women with elevated CRP was higher in HRT users than nonusers (59.2% vs. 34.1%,  $p < 0.01$ ) but was not associated with smoking status. Metabolic syndrome prevalence was not associated with smoking or HRT status. Figure 1 shows a direct association ( $p < 0.0001$ ) between CRP concentration and the number of metabolic syndrome components present. Elevated CRP was strongly associated with metabolic syndrome prevalence in unadjusted (OR = 3.61,  $p = 0.003$ ) and in age-adjusted and race-adjusted (OR = 3.24,  $p = 0.009$ ) logistic regression models (Table 5). Additional adjustments for HRT, BMI, and HOMA-IR did not eliminate the association between CRP and metabolic syndrome ( $p < 0.02$ ). However, adjustment for maximal MET levels of fitness eliminated the association between CRP and metabolic syndrome

(OR = 1.39,  $p = 0.59$ ). In this model, fitness was inversely associated with metabolic syndrome (OR = 0.89, 95% CI = 0.76 to 0.98,  $p = 0.001$ ) even with adjustment for age, race, and CRP.

To examine the implications of our findings on cardiovascular risk, we used a Framingham 10-year probability above the 75th percentile (>6% probability of developing CHD) as a surrogate end point. After adjusting for age and race, women with both high CRP and metabolic syndrome had an increased likelihood (OR = 8.16, 95% CI = 1.61–12.14) of an elevated Framingham score compared with women who had neither risk factor. This association was eliminated when maximal METs was entered in the regression model (OR = 2.9, 95% CI = 0.91–5.97,  $p = 0.20$ ).

## DISCUSSION

Two primary findings resulted from this cross-sectional study. First, a significant direct association between elevated CRP and metabolic syndrome prevalence was observed in the racially diverse cohort of CAPS women, similar to that reported in predominantly white groups of U.S. women.<sup>3,8</sup> Second, we extend existing literature by showing that the association between CRP and metabolic syndrome is eliminated once cardiorespiratory fitness is taken into account. Given that increasing physical activity is a front-line element of the national preventive and therapeutic algorithm for metabolic syndrome,<sup>5</sup> these findings may have important clinical and public health implications.

The prevalence of metabolic syndrome (25%), elevated CRP (46%), and metabolic syndrome combined with elevated CRP (18%) among CAPS women was generally consistent with the preva-

TABLE 4. PROPORTION OF WOMEN WITH ELEVATED CRP AND METABOLIC SYNDROME BY FITNESS

	<i>Fitness</i>				p
	<8.5		≥8.5		
	METs		METs		
	n	%	n	%	
CRP >2.0 mg/L	42	62	22	31	0.0005
Metabolic syndrome	24	35	7	10	0.0004
Elevated CRP and metabolic syndrome	17	25	5	7	0.005



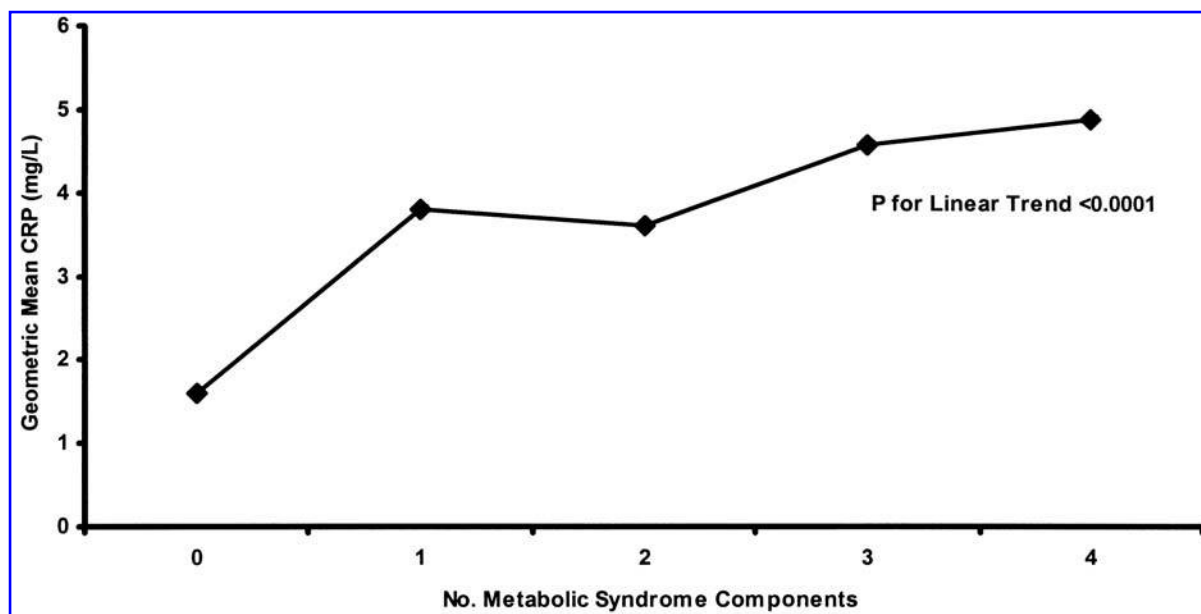


FIG. 1. Race-adjusted geometric mean CRP concentrations (mg/L) according to the number of metabolic syndrome components present in the study sample ( $n = 52, 25, 27, 22$ , and  $9$ , respectively).

lence of these phenotypes (24%, 29%, and 14%, respectively) reported by Ridker et al.<sup>8</sup> (computed from Figure 2, p.394) in a large cohort of healthy, predominantly white women of similar age (54 years) and BMI (27 kg/m<sup>2</sup>) to CAPS women. Although there were differences in the prevalence of elevated CRP owing to differences in case definition, the association of CRP with each metabolic syndrome component and the number of coexisting factors was also very similar between CAPS women and the women reported on by Ridker et al.<sup>8</sup> Ridker et al. showed cardiovascular risk was significantly elevated among women with either metabolic syndrome (RR = 2.3) or CRP >3.0 mg/L (RR = 1.5) over the risk in women without either factor; but the risk was 4-fold higher among women who had both

high CRP and metabolic syndrome.<sup>8</sup> Similar findings were reported recently for cardiovascular and diabetes outcomes in men.<sup>9</sup> We did not have prospective cardiovascular or diabetes events in CAPS. Our observation that the combination of elevated CRP and metabolic syndrome is associated with an 8-fold increase in the relative odds of having above the 75th percentile Framingham score is consistent with the strong direct prospective associations for this phenotype with cardiovascular events reported among women<sup>8</sup> and men.<sup>9</sup> Collectively, available cross-sectional and prospective data underscore the importance of identifying asymptomatic individuals with low-grade inflammation and metabolic syndrome for intensive primary prevention of CVD and diabetes.

TABLE 5. ASSOCIATION BETWEEN CRP AND PREVALENT METABOLIC SYNDROME

Variable in model	Odds ratio <sup>a</sup>	95% CI	p
CRP >2.0 mg/L	3.61	1.54–8.44	0.003
+ age	3.43	1.57–8.83	0.003
+ age + race	3.24	1.58–7.90	0.009
+ HRT <sup>b</sup>	3.79	1.57–9.17	0.003
+ BMI <sup>b</sup>	2.62	1.96–7.13	0.02
+ HOMA-IR <sup>b</sup>	1.82	1.66–5.02	0.02
+ Maximal METs <sup>b</sup>	1.39	0.96–5.91	0.59

<sup>a</sup>Odds ratios are for prevalent metabolic syndrome in women with CRP >2.0 mg/L after adjusting for the specified covariable(s). Women with CRP ≤2.0 mg/L are the referent group.

<sup>b</sup>Entered separately into a model with CRP, age, and race.

National recommendations identify lifestyle modifications, including regular physical activity, as the cornerstone of preventing and treating metabolic syndrome.<sup>5</sup> Accumulating evidence suggests higher levels of physical activity and fitness confer resistance to subclinical inflammation.<sup>11,12</sup> Among CAPS women, maximal cardiorespiratory fitness, an objective marker of recent activity patterns,<sup>16</sup> eliminated the association between elevated CRP and metabolic syndrome, as well as the association of combined elevated CRP and metabolic syndrome with an elevated Framingham score. The latter observation is consistent with prospective data showing higher fitness is related to lower cardiovascular mortality among women.<sup>20</sup> Although cross-sectional in nature, we believe the data reported herein suggest that enhanced cardiorespiratory fitness should be a primary mechanism for preventing increases in health risk associated with vascular inflammation and risk factor clustering, such as metabolic syndrome. Prospective studies in diverse populations of men and women are needed to better understand the degree of penetrance that activity and fitness have in the causal pathway of vascular inflammation and metabolic syndrome with diabetes and CVD.

Several mechanisms have been described that might lower CRP, metabolic syndrome, and their associated adverse risks among active and fit individuals.<sup>10–14,17,20</sup> Potential mechanisms include enhanced natural killer (NK) cell activity against acute vascular infection, improved insulin sensitivity and glycemic control, and lower levels of body fat, circulating catecholamines, and oxidized low-density lipoprotein (LDL) cholesterol. Experimental data are needed to elucidate the specific etiological pathways through which an active and fit lifestyle mediates the long-term risk associated with elevated CRP and metabolic syndrome.

The current study has limitations that should be considered when interpreting and generalizing the findings reported herein. This study was an analysis of data collected during a larger investigation aimed at developing a culturally sensitive physical activity survey rather than examining the complex associations among fitness, CRP, and metabolic syndrome. Consequently, the relatively small sample and cross-sectional design restrict the power of statistical analyses and limit the conclusions and generalizations that can be drawn. Several of the effect estimates were

bound by wide confidence intervals, likely owing to the small sample size and large variance within the data. We believe our analysis is, however, important because it is the first study to consider the influence of fitness on the high-risk phenotype of metabolic syndrome combined with elevated CRP in a racially diverse sample of asymptomatic women. We recognize that a modest genetic transmission contributes to individual levels of cardiorespiratory fitness.<sup>21</sup> However, reported exercise training gains of up to 30% and rapid detraining-related losses<sup>22</sup> illustrate the plasticity of cardiorespiratory fitness and should temper genetic arguments against targeting fitness enhancement as a part of disease prevention. We would hope that our cross-sectional data stimulate the design of large prospective analyses to provide more definitive data on the influence of fitness on elevated CRP and metabolic syndrome.

We conclude that elevated CRP is strongly associated with prevalent metabolic syndrome among racially diverse women. Higher levels of cardiorespiratory fitness appear to favorably influence the association between CRP and metabolic syndrome. This observation may be a mechanism of cardioprotection associated with an active and fit lifestyle and is further support for current recommendations promoting physical activity and fitness in the primary prevention of cardiovascular and related diseases.

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